REMARKS

In the parent case, Application No. 10/354,521, ("parent case") an Office Action was mailed on September 10, 2003 rejecting claims 1, 9, 10 and 16-19 ("Office Action"). Applicants have separately responded to the Office Action in the parent, and pursue additional subject matter in this continuation application.

Applicants have cancelled claims 4-8 without prejudice. Applicants have also amended claims 1-3, 9, 10 and 16, 17, 19 and 20 to recite the preferred crystalline tiotropium bromide monohydrate (such as monoclinic crystalline tiotropium bromide monohydrate, See, e. g., Specification, pp. 8-9).

Reconsideration and allowance of the pending claims is respectfully requested.

In the Office Action, claim 17 was rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for treating diseases beyond "asthma and COPD" according to the standards set in In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988). Claims 16 and 17 were rejected under 35 U.S.C. 112, second paragraph, as being "indefinite" for the recitation of the term "effective amount" because the amount is alleged to be "critical". Claim 17 was rejected for the phrase "may have a therapeutic benefit". Applicants respectfully traversed those rejections.

Anticholinergic agents are well known medicaments for a wide variety of diseases and disorders, including, *inter alia*, inflammatory disorders (biperiden), gastrointestinal disorders (dicyclomine), urinary disorders (oxybutynin), allergic disorders (ipratropium), respiratory disorders (ipratropium) and CNS disorders (atropine). The state of the art is furthermore, well known regarding the use of anticholinergic agents as medicaments, not to mention the well known dosage forms, routes of administration, dosage regimens, and dosage strengths, including applicants' own disclosures (See, e. g., Index from Conn's Current Therapy – 2003 for Anticholinergics [listing, *inter alia*, allergic rhinitis, asthma, COPD, extrapyramidal symptoms, IBS, nausea and vomiting, and urge incontinence] and questions from Chapter 21 from the web site

connection.lww.com/Products/abrams/documents/Review Application/RAE-Ch21.doc, citing, *inter alia*, GI, GU, ophthalmic and respiratory disorders, copy attached). Moreover, once the agent is identified, the dosage form and strength can be adjusted by the ordinarily skilled medical practitioner without undue experimentation depending on the therapeutic endpoint for the specific medical complication to be treated.

Accordingly, the amendment of claims 16 and 17, respectively, to recite "effective therapeutic amount" of the crystalline tiotropium bromide monohydrate is believed to overcome the rejection under 35 U.S.C. 112, first and second paragraphs.

Accordingly, those rejections under Section 112 should be reconsidered.

In the Office Action, claims 1, 9, 10 and 16-19 were rejected under 35 U.S.C. 103(a) as obvious over Banholzer et al, SI 9011744 B, in view of Banholzer et al, EP 0418716 B1, and Banholzer et al, US 5,610,163. In particular, it was alleged that (a) '744 B teaches a novel tiotropium compound, its salts and hydrates (including tiotropium bromide hydrate), cataloged at 139404-48-1, useful as an anti-asthmatic and to treat pulmonary obstructive disease, (b) '716 B teaches quaternary salts of tiotropium bromide, and (c) '163 teaches the quaternary salts of tiotropium bromide in an inhalable powder, rendering claims 1, 9, 10 and 16-19 prima facie obvious. Applicants respectfully traversed that rejection.

The invention relates to a novel modification of the compound, tiotropium bromide, and to methods for making it. In particular, the invention relates to novel crystalline modifications of tiotropium bromide described as crystalline tiotropium bromide monohydrate and monoclinic crystalline tiotropium bromide monohydrate. Such crystalline compounds may be obtained by selecting specific reaction conditions (See, e. g., Specification, p. 5) to improve physical and chemical stability necessary for yielding pharmaceutically and commercially useful compounds.

SI 9011744 B, cited by the Examiner as disclosing "a novel tiotropium bromide compound, and its salts and hydrates" in fact discloses only acid addition

salts of tiotropium, similar in scope to the compounds disclosed in the other cited references (a true English language translation of originally filed claims of SI 9011744 B, along with red-lined amendments, is enclosed). Accordingly, SI 9011744 B nowhere discloses or suggests crystalline modifications to tiotropium bromide, let alone specifically the claimed monoclinic crystalline tiotropium bromide monohydrate form, nor to methods for making particular crystalline structures. Thus, SI 9011744 B is merely cumulative of the other cited references (EP 0418716B and US 5,610,163), none of which disclose or suggest crystalline forms of tiotropium bromide or methods for obtaining them.

Moreover, though recognizing "that neither the '744 application nor the '716 or '163 patents employ tiotropium bromide or its hydrate in crystalline form", the Examiner misses the salient point that none of the references refer to or suggest any crystalline form of tiotropium whatsoever, let alone the monoclinic form. Furthermore, the naked proposition that the production of crystal forms of chemicals and pharmaceuticals "has long been the practice" is insufficient standing alone to render the pending claims prima facie obvious. That the claimed compounds may be desirable, or obvious to try to make, does not render the actual creation a foregone conclusion. That is, the claimed monohydrate is a pseudopolymorph of tiotropium bromide which required empirical evidence to determine whether it could be produced in stable form. (See, also, SmithKline Beecham Corp. v. Apotex Corp., 247 F.Supp.2d 1011, 1016-1017 (N.D. Ill. Mar. 3, 2003) (No. 98 C 3952) [recognizing the separate patentability of a crystalline form of paroxetine hemihydrate over the amorphous form]. Accordingly, the Examiner's basis for alleging that the claims to crystalline tiotropium bromide monohydrate or to monoclinic crystalline tiotropium bromide monohydrate, such as presented in new claim 2, are prima facie obvious is unsupported by the cited documents. In light of the circumstances, the rejection of claims 1, 9, 10 and 16, 17 and 19 under Section 103 should be reconsidered.

Applicants note the obviousness-type double patenting rejection of method claims 16-19 over claims 1-5 and 11-16 of the cited '163 patent in view of '744 B. That rejection, in light of the comments and amendments presented herein, should be reconsidered.

Early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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